REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

The claims have been amended without prejudice to require that the ubiquitous promoter is a polymerase III dependent promoter. As a result, references to the CMV and CAGGS promoters have been deleted.

Claims 8, 18 and 19 have been canceled.

Also, the phrase "non-human vertebrate," wherever it appears has been amended to -- mouse --.

Finally, an editorial change has been made in claim 22.

Applicants do not believe that any of these amendments introduce new matter. An early notice to that effect is earnestly solicited.

Claim 1 was objected to due to an informality. In response, Applicants have corrected claim 1, and, also, claim 26.

Claims 1, 5, 6, 8-12, 15-24, 26 and 27 were rejected under 35 USC § 112, first paragraph, as being broader than the enabling disclosure. In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The Examiner throughout his rejection speaks of the unpredictability in knockout results in the prior art, and the need for experimentation to prove the usefulness of particular constructs. However, Applicants respectfully submit that neither any

unpredictability nor any need for experimentation, in and of themselves, justifies a lack of enablement position. For, as pointed out in MPEP § 2164.01(a):

> "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. * * * The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue."

Indeed, as the Court in *In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), explained, "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." Further, on the same page, they quoted with approval the following quote from *In re Jackson,* 217 USPQ at 807 (POBA 1982):

> "The test [for undue experimentation] is not merely quantitative, since a ***considerable*** amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction the experimentation should take. [Emphasis added.]"

The Examiner has not included the constructs in this rejection and, therefore, there is no issue that persons skilled in the art are enabled to make such constructs.

The issue is whether persons skilled in the art are enabled to use such constructs without undue experimentation. Applicants respectfully submit that they are and, moreover, that the instant specification provides reasonable guidance to that end.

The instant examples teach persons skilled in the art how to take those constructs and stably integrate them into the genome of the mouse, and to test and confirm whether a reduction in the activity of the target gene has been obtained. Applicants respectfully submit that these teachings are sufficient as a matter of law to enable the full scope of the claimed invention, predictability and experimentation issues notwithstanding.

Taking the latter first, persons skilled in the art can take any such construct and integrate and test according to the teachings of the instant specification. Certainly, this will require some experimentation, but all such experimentation is simply routine experimentation and, therefore, is not undue experimentation. See, again, the quote from Jackson supra: "[A] ***considerable*** amount of experimentation is permissible, if it is merely routine." The Examiner has not shown any alleged experimentation required here to be anything other than routine experimentation. Accordingly, Applicants respectfully submit that any required experimentation is not, in fact, undue experimentation.

Next, the Examiner at various points implies that the instant claims are not limited to any particular phenotype. Applicants respectfully disagree. Main claim 1 requires that the integration of the construct into the mouse genome results in "a reduction in the activity of a product of [the target] gene." In a similar manner, claim 37 requires "an at least 30% reduction in the activity of an expression product of said gene."

Two important things flow from such requirements: First, the resulting transgenic mouse is, in fact, phenotypically different from the naïve mouse lacking such construct in that the transgenic mouse will exhibit a reduced activity in the product of the target gene compared to the naïve mouse.

Second, the claimed method is exactly tailored to the enablement. The reduction in product activity is positively recited, which means that embodiments where no such product activity is achieved *are expressly excluded from the claims.* In other words, the claims do *only* embrace *fully operative* embodiments.

Thus, the Examiner's theories about what might happen if this should be done and that should be done are, respectfully, irrelevant since even if the Examiner is correct, the claims exclude such clearly inoperative results.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. The enabling disclosure is reasonably commensurate in scope with the claims, particularly in view of the positive functional requirements of successful results in reducing the activity of a product of the target gene. An early notice that this rejection has been reconsidered and withdrawn is, therefore, earnestly solicited.

Claims 1, 5, 6, 8-10, 15, 16, 18, 20-24, 26, 27 and 30 were rejected under 35 USC § 103(a) as being obvious over McCaffrey et al. ("McCaffrey"), *Nature, 418:* 38-39 (2002), or Beach et al. ("Beach"), US 2003/0084471, and Bronson et al. ("Bronson"), *Proc. Natl. Acad. Sci. USA, 93:* 9067-9072 (1996).

Claims 1, 5, 27 and 30 were rejected under 35 USC § 103(a) as being obvious over McCaffrey or Beach and Bronson in view of Soriano et al. ("Soriano"), US 6,461,864.

Claims 11, 12, 17 and 19 were rejected under 35 USC § 103(a) as being obvious over McCaffrey or Beach and Bronson in view of Soriano and further in view of Ohkawa et al. ("Ohkawa"), *Hum. Gene Ther., 11:* 577-85 (2000).

Claims 31-35, 37 and 38 were rejected under 35 USC § 103(a) as being obvious over McCaffrey or Beach and Bronson in view of Soriano and Kunath et al. ("Kunath"), Nature Biotech., 21: 559-561 (2003).

In response to ***all*** of the obviousness rejections, which are based primarily in each case on the combination of McCaffrey or Beach and Bronson, Applicants respectfully submit that the cited combination of references does not make out a *prima facie* case of the obviousness of any of the current claims. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw each of these rejections.

As noted above, Applicants have amended the previous claims without prejudice to require that the shRNA construct be under the control of a ubiquitous polymerase III dependent promoter and be integrated into a polymerase II dependent locus of the mouse genome. As is apparent from the instant examples, Applicants have found that a single copy shRNA construct under the control of a polymerase III dependent promoter can mediate ubiquitous RNA interference in a living organism when integrated into a RNA polymerase II dependent locus. And, as discussed in the instant specification in the second paragraph on page 2 and the second paragraph on page 3, this finding was by no means obvious to persons having ordinary skill in the art. The combinations of McCaffrey or Beach and Bronson alone or further in view of Soriano, Ohkawa and/or Kunath do not teach or suggest to persons having ordinary skill in the art a single copy shRNA construct under the control of a polymerase III dependent promoter can mediate ubiquitous RNA interference in a living organism when integrated into a RNA polymerase II dependent locus. Consequently, Applicants respectfully submit that the various cited combinations of

these references do not make out a *prima facie* case of the obviousness of any of the rejected claims.

Taken together, McCaffrey, Beach and Kunath teach a method of gene knockdown in a mouse by administering a shRNA expression vector. However, these references are not instructive in respect to the strategy of targeted integration of an shRNA construct under the control of a polymerase III dependent promoter into a RNA polymerase II dependent locus to achieve ubiquitous RNA interference in a living organism.

McCaffrey demonstrates transient inhibition of gene expression by injection of purified siRNA or a plasmid encoding a shRNA expression vector into the tail vain of mice. Using this approach, gene knockdown is restricted to the liver and persists only a few days. Although the result demonstrates that the mechanism of RNAi mediated gene silencing is functional in mice, the reference not instructive for transgenic shRNA expression.

Beach demonstrates that a luciferase specific shRNA under the control of the U6 promoter can mediate widespread gene silencing in cultured cell lines (referred as '*in vivo*' in this document). Random rather than targeted integration of shRNA expression vectors is applied in all experiments presented by Beach and the resulting cell lines were not further analyzed in respect to the integration site or the number of shRNA copies integrated into the genome. Usually, random integration of DNA vectors results in a concatameric array of multiple copies, whereas single copy integrations are unusual (Martin & Whitelaw 1996, BioAssays 18, p. 919-923).

Kunath demonstrated shRNA-mediated silencing of RasGAP using a shRNA construct under the control of the human H1 promoter in transgenic mice. Experiments presented in the document included random integration of shRNA transgenes resulting in variable levels and patterns of shRNA expression. Ubiquitous expression of the shRNA vector is not revealed.

The lack of information in Beach/McCaffrey/Kunath concerning ubiquitous expression of shRNA transgenes in a multicellular organism is not cured by Bronson. Particularly, Bronson did not provide motivation of targeting an shRNA construct under the control of a RNA polymerase III dependent promoter into to a RNA polymerase II dependent locus.

Bronson applied homologous recombination at the HPRT locus to introduce a *bcl-2* cDNA under the control of a RNA polymerase II dependent promoter (chicken and human ß-actin). The expression level of the targeted *bcl*-2 transgenes appeared to be non-ubiquitous and varied between the two different constructs. Therefore, the data suggest that targeted integration into a ubiquitously active locus (such as *hprt*) does not promote ubiquitous expression of a transgene under the control of a RNA polymerase II dependent promoter. The activity of an shRNA construct under the control of a RNA polymerase III dependent promoter is not revealed by the reference.

The lack of information in Beach/McCaffrey/Bronson/Kunath concerning the activity of shRNA transgenes under the control of an RNA polymerase III dependent promoter when integrated into a RNA polymerase II dependent locus is not provided by Soriano either. Soriano describes a method for the production of transgenic animals,

which ubiquitously express a heterologous gene inserted into the Rosa26 locus through homologous recombination. In this configuration, the endogenous rosa26 promoter drives transgene expression via a splice acceptor sequence. Therefore, Soriano suggests targeted integration of a promoter-less transgene benefit from the activity of the endogenous promoter. However, Soriano did not examine the activity of an exogenous promoter that is stably integrated at *rosa26*.

Consequently, considering the foregoing, there is no teaching or suggestion in any of the cited combinations of references that a single copy shRNA construct under the control of a polymerase III dependent promoter can mediate ubiquitous RNA interference in a living organism when integrated into a RNA polymerase II dependent locus. Thus, Applicants respectfully submit that the various cited combinations of these references do not make out a *prima facie* case of the obviousness of any of the rejected claims.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw all of the foregoing obviousness rejections. An early notice that these rejections have been reconsidered and withdrawn is earnestly solicited.

Claims 1, 5, 6, 8-12, 15-24, 26, 27 and 30 were provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 14-16 and 18-44 of copending application Serial No. 10/531,347. In response, Applicants continue to request that this issue be held in abeyance until allowable subject matter is indicated, at which time Applicants will take appropriate action, for example, prove patentable distinctness or file a suitable terminal disclaimer.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,

NORRIS McLAUGHLIN & MARCUS, P.A.

By /Kurt G. Briscoe/

Kurt G. Briscoe
Attorney for Applicant(s)
Reg. No. 33,141
875 Third Avenue - 18th Floor
New York, New York 10022
Phone: (212) 808-0700
Fax: (212) 808-0844